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Original Article

Effect of fexofenadine on the quality of life of Japanese cedar pollinosis patients

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Abstract

Background: The aim of the present survey was to investigate the changes associated with fexofenadine administration in the quality of life (QOL) of Japanese cedar pollinosis patients.

Methods: After obtaining informed consent, volunteers suffering from Japanese cedar pollinosis were divided into two groups: (i) the fexofenadine group (2 × 60 mg/day); and (ii) the placebo group. Changes in QOL were examined after administration for 14 days (randomized, double-blind comparison study). The study period was from 27 February to 13 March 2003. Subjects were recruited from the Tokyo metropolitan area; 104 were randomized to the fexofenadine group and 103 were randomized to the placebo group. The QOL was evaluated using the Japanese Allergic Rhinitis Standard QOL Questionnaire (JRQLQ no. 1). The JRQLQ is structured to evaluate six domains of usual daily activities, outdoor activities, social functioning, sleep problems, general physical problems and emotional function, as well as the overall QOL.

Results: On the 14th day after the start of fexofenadine or placebo administration, the QOL was improved in all domains of the JRQLQ in the fexofenadine group, whereas it had worsened in all domains, except outdoor activities, in the placebo group. The overall evaluation of QOL was significantly more favorable in the fexofenadine group on the 14th day after the start of administration.

Conclusions: The present study showed that fexofenadine administration suppressed the deterioration of overall QOL and alleviated the interference with daily life in patients suffering from Japanese cedar pollinosis.

Key words: allergic rhinitis, cedar pollinosis, daily life, fexofenadine, quality of life.

Introduction

Allergic rhinitis does not threaten life directly, but it has a significant impact on the quality of life (QOL) and sometimes restricts the daily activity of patients. Furthermore, allergic rhinitis symptoms influence study and work conditions, inflicting a significant burden socially and economically. In Japan, approximately 15% of the population nationwide suffers from cedar pollinosis.[1]

Many types of therapy are used for the treatment of allergies, including pollinosis. Among the most frequently used pharmacotherapies, antihistamines are often the drugs of choice. Antihistamines relieve symptoms, but they do not cure the disease. With antihistamines, patients can spend their daily life more comfortably and productively.

Fexofenadine HCl was approved as an antihistamine against allergies in September 2000 in Japan and it is currently used widely. Abroad, it has been approved in 102 countries, including the US, UK, France and Germany, and, as of March 2000, fexofenadine HCl was marketed in 57 countries.

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In the present study, the QOL of Japanese cedar pollinosis patients was evaluated, in comparison with a placebo control, using the 'Japanese Allergic Rhinitis QOL Standard Questionnaire' (JRQLQ) after administration of 60 mg fexofenadine HCl, twice daily for 14 days.

METHODS

Patients

The subjects were male and female Japanese cedar pollinosis patients (hereafter called 'patients') aged from 20 to 56 years. Cedar pollinosis symptoms had to have been present for more than 2 years and cedar pollen-specific IgE was class 2 or above. Patients who lived or worked in the metropolitan area were favored as study subjects. In addition, the total symptom score (TSS; comprising sneezing, runny nose, nasal congestion, itchy eyes and watery eyes) was at least 4 and at least two of the five symptoms were of greater than moderate severity on the starting day of administration.

The following patients were excluded from the study: patients whose symptoms had developed before the cedar pollen season, patients with complications of nasal diseases that could have an effect on the evaluation of efficacy (perennial allergic rhinitis, acute and chronic rhinitis etc.), patients who planned to go to Hokkaido, Okinawa or abroad, and others whom the physician-in-charge judged unfit as study subjects.

Prior to participation in the present study, written consent was obtained from all patients after the physician-in-charge had explained the study in person to the patients. In addition, the study was conducted with the approval of the Institutional Review Board of Nippon Medical School.

Study design

The present study was a randomized, double-blind comparison study against a placebo control, performed at a single institution.

After obtaining patient consent, screening was performed to confirm compliance with the subject selection and exclusion criteria and to examine the physical condition of each individual. Screening included patient background, physician's examination, clinical laboratory analysis (hematology, blood biochemistry, serology and urinalysis), physical examination, and electrocardiogram (12 lead electrocardiogram). The physician-in-charge determined the eligibility of each patient as a subject in the present study based on the results of screening. The pre-observation period was 7 days before the start of administration of the trial drug, during which time the physician's examination, rhinoscopy and blood collection were performed. Following completion of the pre-observation period, patients were assigned at random to receive test drug or placebo and administration was started. A fexofenadine HCl 60 mg tablet (fexofenadine group) or placebo tablet (placebo group) was administered twice a day, once in the morning and once in the evening, for 14 days (Fig. 1).

Patients were asked to record in the patient diary pollinosis symptoms (sneezing, runny nose, nasal congestion, itchy eyes, watery eyes and interference with daily life) and compliance with the drug administration schedule.

The physician-in-charge examined each patient a total of five times: at screening, during the pre-observation period, on the starting day of drug administration and 1 and 2 weeks after the start of drug administration. The baseline data were those at the start of drug administration and the end-points were data obtained 2 weeks after the start of test drug administration.

Patients were asked to fill out the JRQLQ questionnaire[2] at the start of the pre-observation period, on the starting day of drug administration and at the times of hospital visits, 1 and 2 weeks after the start of drug administration (Fig. 2). In addition, patients were asked to make an entry in the patient diary every day from the start of the pre-observation period until the day after the completion of drug administration.

During the study period, any concurrent use of drugs that could influence the evaluation of efficacy was prohibited. However, when drugs had to be used, as judged by the physician-in-charge, the drugs used were recorded in the survey form.

Evaluation items

The JRQLQ

The JRQLQ, which was used as the primary standard for evaluation, is composed of three parts: nasal and eye symptoms (JRQLQ I), a QOL-related questionnaire (JRQLQ II) and an overall face scale.

The nasal and eye symptoms included the six categories of runny nose, sneezing, nasal congestion, itchy nose, itchy eyes and watery eyes. Each subject evaluated symptoms on a five-point scale, which included 0 for no symptoms, 1 for mild, 2 for moderately severe, 3 for severe and 4 for very severe symptoms. Mean scores for

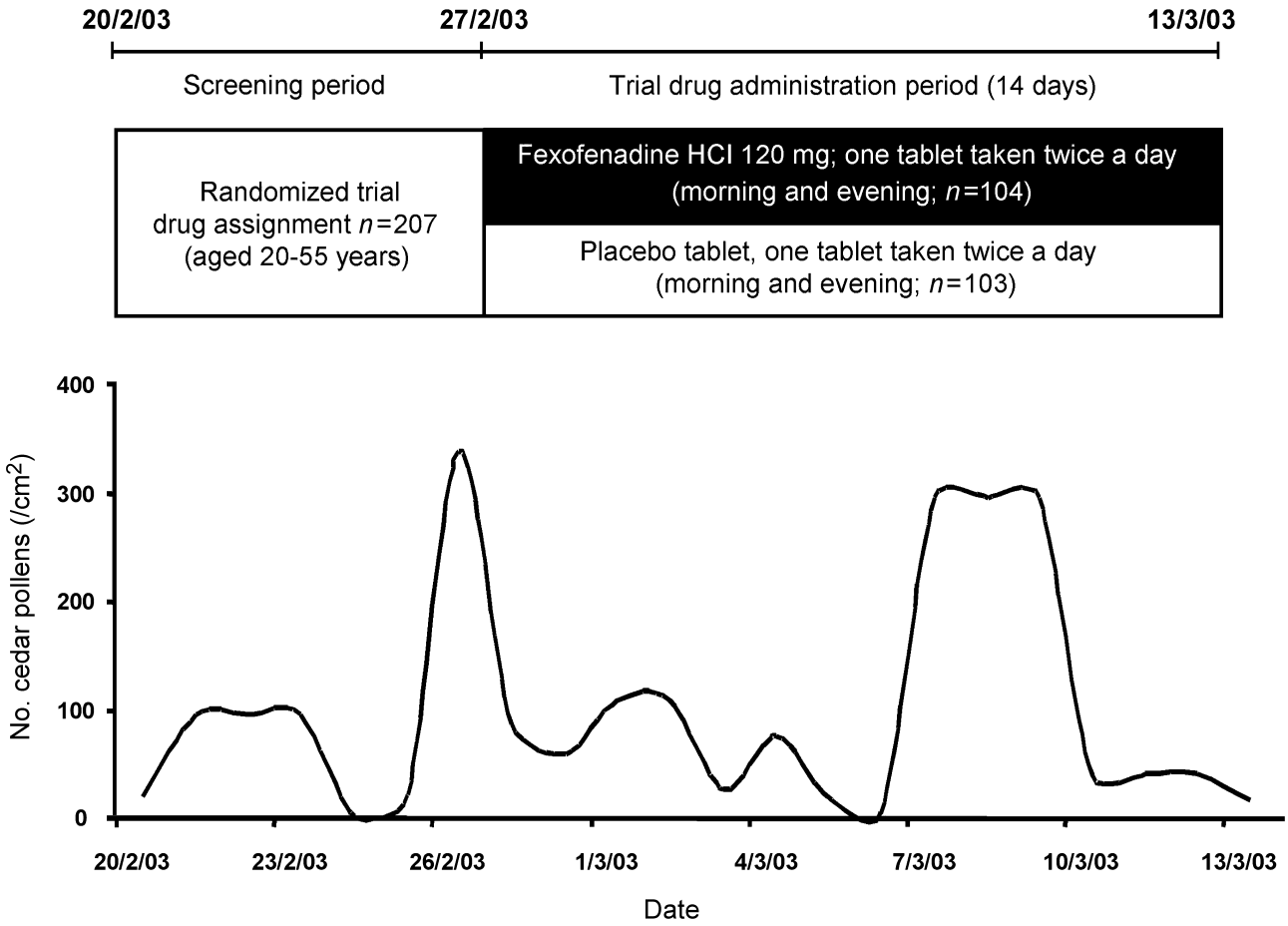


Fig. 1 Study design.

these six categories were determined as the mean nasal and eye symptom scores (JRQLQ I).

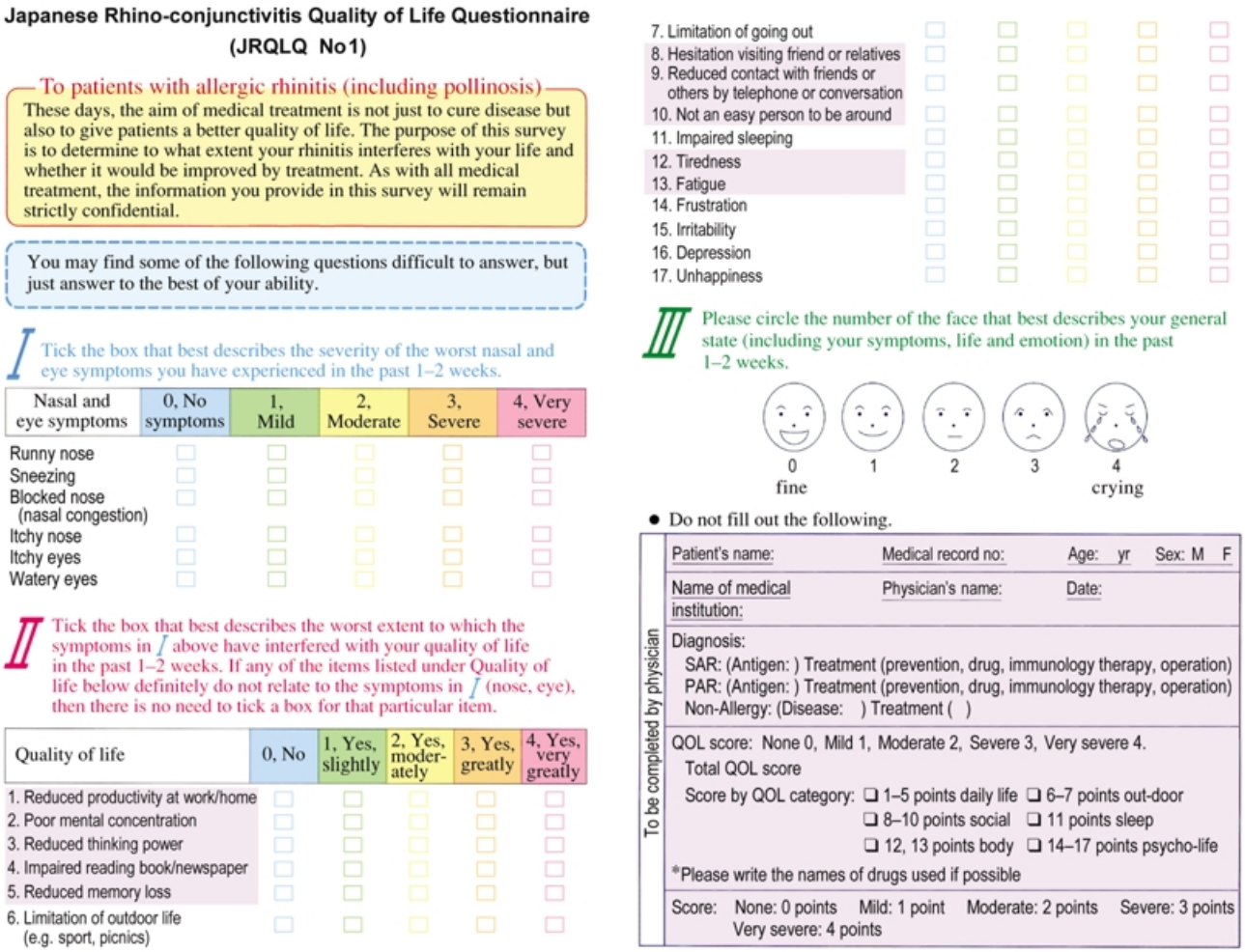
The QOL-related questionnaire included 17 items concerning: (i) reduced productivity at work/home/school; (ii) poor mental concentration; (iii) reduced thinking power; (iv) impaired reading book/paper; (v) reduced memory loss; (vi) limitation of outdoor life (e.g. sports, picnic); (vii) limitation of going out; (viii) hesitation visiting friend or relatives; (ix) reduced contact with friends or others by telephone or conversation; (x) not an easy person to be around; (xi) impaired sleeping; (xii) tiredness; (xiii) fatigue; (xiv) frustration; (xv) irritability; (xvi) depression; and (xvii) unhappiness. Each item was evaluated on a five-point scale as 0 for no significant problem, 1 for a mild problem, 2 for moderately severe, 3 for severe and 4 for very severe (Fig. 2). Mean scores for these categories were determined as the mean QOL-related questionnaire scores (JRQLQ II). In addition, these categories were divided into six domains, including 'usual daily activities' for items i–v, 'outdoor activities' for items vi and vii, 'social functioning' for items viii to x, 'sleep problem' for item xi, 'general physical problems' for items xii and xiii, and 'emotional function' for items xiv to xvii. The mean score for each domain was calculated for analysis.

Overall face scale, including overall symptoms, condition and feelings, was evaluated on a scale from 0 for 'happy' to 4 for 'crying' for the past 1–2 weeks.[2]

The present study evaluated the mean score for each domain in the QOL-related questionnaire as well as JRQLQ I, JRQLQ II and overall face scale.

Allergy diary

In the allergy diary, each item from a list including sneezing (number of attacks in a day), runny nose (number of incidences of nose blowing per day), nasal congestion, itchy eyes and watery eyes was evaluated on



Japanese Rhino-conjunctivitis Quality of Life Questionnaire (JRQLQ No1)

To patients with allergic rhinitis (including pollinosis)

These days, the aim of medical treatment is not just to cure disease but also to give patients a better quality of life. The purpose of this survey is to determine to what extent your rhinitis interferes with your life and whether it would be improved by treatment. As with all medical treatment, the information you provide in this survey will remain strictly confidential.

You may find some of the following questions difficult to answer, but just answer to the best of your ability.

I Tick the box that best describes the severity of the worst nasal and eye symptoms you have experienced in the past 1–2 weeks.

Nasal and eye symptoms	0, No symptoms	1, Mild	2, Moderate	3, Severe	4, Very severe
Runny nose	☐	☐	☐	☐	☐
Sneezing	☐	☐	☐	☐	☐
Blocked nose (nasal congestion)	☐	☐	☐	☐	☐
Itchy nose	☐	☐	☐	☐	☐
Itchy eyes	☐	☐	☐	☐	☐
Watery eyes	☐	☐	☐	☐	☐

II Tick the box that best describes the worst extent to which the symptoms in I above have interfered with your quality of life in the past 1–2 weeks. If any of the items listed under Quality of life below definitely do not relate to the symptoms in I (nose, eye), then there is no need to tick a box for that particular item.

Quality of life	0, No	1, Yes, slightly	2, Yes, moderately	3, Yes, greatly	4, Yes, very greatly
1. Reduced productivity at work/home	☐	☐	☐	☐	☐
2. Poor mental concentration	☐	☐	☐	☐	☐
3. Reduced thinking power	☐	☐	☐	☐	☐
4. Impaired reading book/newspaper	☐	☐	☐	☐	☐
5. Reduced memory loss	☐	☐	☐	☐	☐
6. Limitation of outdoor life (e.g. sport, picnics)	☐	☐	☐	☐	☐
7. Limitation of going out	☐	☐	☐	☐	☐
8. Hesitation visiting friend or relatives	☐	☐	☐	☐	☐
9. Reduced contact with friends or others by telephone or conversation	☐	☐	☐	☐	☐
10. Not an easy person to be around	☐	☐	☐	☐	☐
11. Impaired sleeping	☐	☐	☐	☐	☐
12. Tiredness	☐	☐	☐	☐	☐
13. Fatigue	☐	☐	☐	☐	☐
14. Frustration	☐	☐	☐	☐	☐
15. Irritability	☐	☐	☐	☐	☐
16. Depression	☐	☐	☐	☐	☐
17. Unhappiness	☐	☐	☐	☐	☐

III Please circle the number of the face that best describes your general state (including your symptoms, life and emotion) in the past 1–2 weeks.

0 fine 1 2 3 4 crying

● Do not fill out the following.

To be completed by physician

Patient's name: Medical record no: Age: yr Sex: M F

Name of medical institution: Physician's name: Date:

Diagnosis:
SAR: (Antigen:) Treatment (prevention, drug, immunology therapy, operation)
PAR: (Antigen:) Treatment (prevention, drug, immunology therapy, operation)
Non-Allergy: (Disease:) Treatment ( )

QOL score: None 0, Mild 1, Moderate 2, Severe 3, Very severe 4.
Total QOL score
Score by QOL category: ❑ 1–5 points daily life ❑ 6–7 points out-door
❑ 8–10 points social ❑ 11 points sleep
❑ 12, 13 points body ❑ 14–17 points psycho-life
*Please write the names of drugs used if possible

Score: None: 0 points Mild: 1 point Moderate: 2 points Severe: 3 points
Very severe: 4 points

Fig. 2 Japanese Allergic Rhinitis Standard Quality of Life Questionnaire (JRQLQ no. 1).

a scale from 0 for the most mild to 4 for the most severe. The total scores for sneezing, runny nose, nasal congestion, itchy eyes and watery eyes were calculated as the TSS for statistical analysis. The severity in the season was compared between the fexofenadine and placebo groups.

Safety

All unfavorable signs and symptoms observed during the period of administration of the test drug were classified as adverse events, regardless of the presence or absence of a causal relationship to the test drug.

The safety items evaluated included analysis of data obtained during the study period (clinical laboratory analysis, physical examination and physician's examination) and symptoms experienced during the study period (only adverse events reported at the physician's examinations, but not those described in the allergy diary).

Statistical analysis

Continuous variables and categorical variables were analyzed by the Mann–Whitney *U*-test and Chi-squared test, respectively, for characteristics related to patients' background (age, sex, address, occupation and work place).

Changes in JRQLQ scores from baseline were analyzed by analysis of covariance (ANCOVA), with the treatment group as the main effect and the baseline values as the covariate. For TSS, the statistical significance between two groups was examined using the Mann–Whitney *U*-test.

RESULTS

Patient population

Of a total of 250 subjects screened, 210 were randomized to receive treatment; 104 received fexofenadine HCl 60 mg b.i.d. (fexofenadine group) and 103 received placebo b.i.d. (placebo group). All 207 randomized subjects completed the 2 week study period.

Overall, 207 subjects were enrolled in the Intent-to-Treat (ITT) population (patients who received at least one dose of treatment and completed a baseline and not less than one valid QOL assessment): 104 subjects in the fexofenadine group and 103 in the placebo group. There were no differences between the two treatment groups in terms of demographic characteristics (Table 1). The mean age of subjects in the fexofenadine group was 32.7 years compared with 34.2 years in the placebo group. The majority of patients were male (60% fexofenadine group; 56% placebo group). There were almost equal numbers of students (47% fexofenadine group; 45% placebo group) and non-students (53% fexofenadine group; 55% placebo group).

Baseline JRQLQ scores were comparable between the two treatment groups (Table 2). The mean QOL-related questionnaire score (JRQLQ II) was 1.00 in the fexofenadine group and 0.89 in the placebo group, showing that patients were greatly troubled by pollinosis symptoms. Individual JRQLQ domain scores at baseline indicated that patients were less troubled by their symptoms in relation to their social functioning and were more troubled in their usual daily activities, outdoor activities and by general physical problems.

Table 1 Patient characteristics at baseline (Intent-to-Treat population)

Characteristic	Fexofenadine HCl 60 mg b.i.d (n = 104)	Placebo (n = 103)	P
Mean (±SD) age (years)	32.7 ± 9.8	34.2 ± 9.8	0.631*
Sex			
Total	104	103	
No. males (%)	62 (60)	58 (56)	0.674†
No. females (%)	42 (40)	45 (44)	
Occupation			
No. students (%)	48 (47)	45 (45)	0.769†
No. non-students (%)	55 (53)	56 (55)	

*Wilcoxon test.

†Chi-squared test.

Table 2 Baseline Japanese Allergic Rhinitis Standard Quality of Life Questionnaire (JRQLQ) scores (Intent-to-Treat population)

Scores	Fexofenadine HCl 60 mg b.i.d (n = 104)	Placebo (n = 103)	P (Wilcoxon test)
Nasal and eye symptoms	1.60 ± 0.73	1.60 ± 0.73	0.864
QOL-related questionnaire	1.00 ± 0.86	0.89 ± 0.73	0.557
Scores by domain			
Usual daily activities	1.19 ± 1.0	0.96 ± 0.8	0.123
Outdoor activities	1.03 ± 1.0	1.08 ± 1.0	0.682
Social functioning	0.66 ± 0.8	0.64 ± 0.7	0.75
Sleep problem	0.93 ± 0.9	0.83 ± 0.9	0.285
General physical problems	1.12 ± 1.1	0.96 ± 1.0	0.495
Emotional function	0.96 ± 1.0	0.87 ± 0.9	0.993
Condition of past 1 or 2 weeks	2.46 ± 0.9	2.45 ± 0.9	0.961

Data are the mean ±SD.

QOL, quality of life.

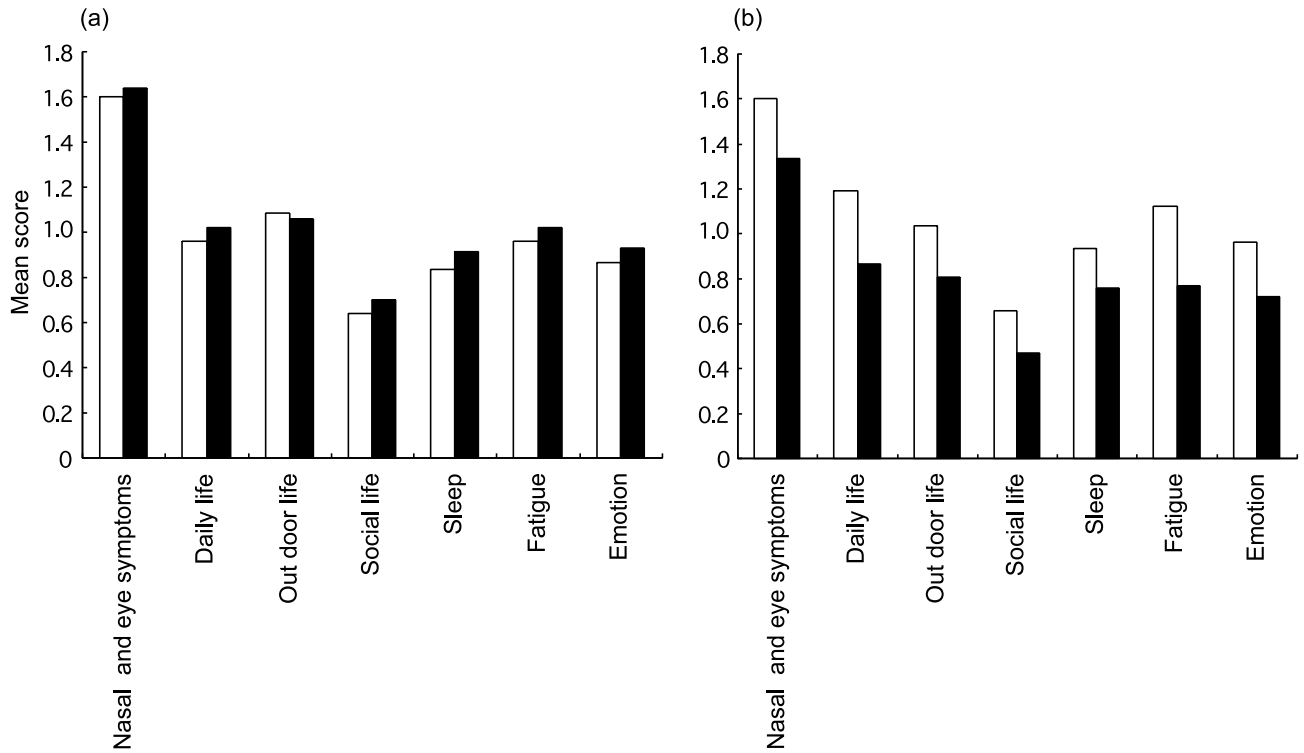


Fig. 3 Mean Japanese Allergic Rhinitis Standard Quality of Life Questionnaire (JRQLQ) scores at baseline (□) and at the end of the 2 week administration period (■) for (a) placebo and (b) fexofenadine HCL 120 mg (60 mg b.i.d.).

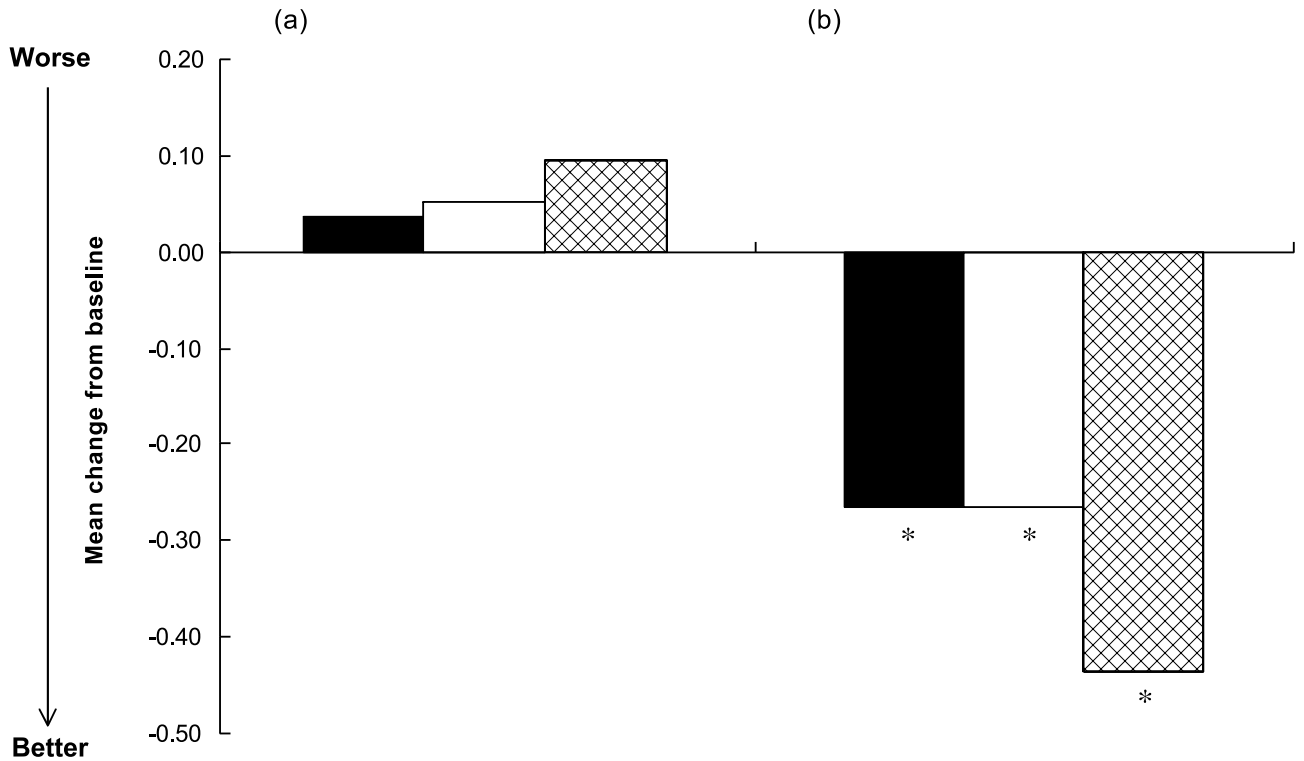


Fig. 4 Mean changes in scores from baseline (■, nasal and eye symptoms; □, quality of life-related questionnaire; ⊠, overall face scale) following 2 week administration of (a) placebo or (b) fexofenadine HCL 120 mg (60 mg b.i.d.). *$P < 0.001$ compared with placebo.

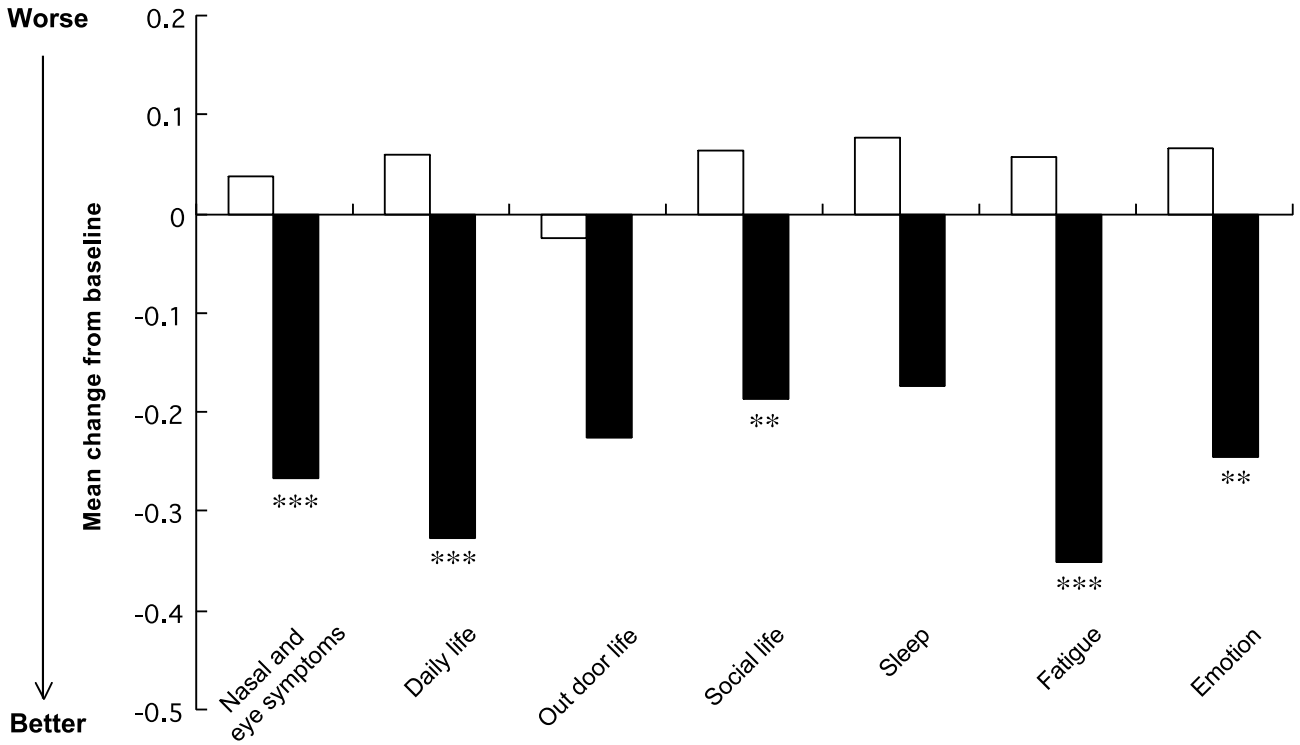


Fig. 5 Mean changes in scores from baseline (domains in the quality of life-related questionnaire) following 2 weeks administration of placebo (□) or fexofenadine HCL 120 mg (60 mg b.i.d.; ■). Changes in nasal and eye symptoms, which are shown in Fig. 4, are shown as a reference. $^{**}P < 0.01$, $^{***}P < 0.001$ compared with placebo.

Outcome

Quality of life

Mean scores in each domain are shown for JRQLQ I and JRQLQ II in Fig. 3. Scores of all domains, except outdoor activities, decreased or worsened in the placebo group, whereas all showed an improvement in the fexofenadine group.

Significant improvements in scores from baseline were clearly seen in the fexofenadine group for JRQLQ I, JRQLQ II and the overall face scale ($P < 0.001$; Fig. 4). In addition, with regard to each domain of JRQLQ II, a significant improvement in scores was observed for usual daily activities ($P < 0.001$), social functioning ($P = 0.002$), general physical problems ($P < 0.001$) and emotional function ($P = 0.002$) in the fexofenadine group (Fig. 5). Scores for outdoor activities ($P = 0.055$) and sleep problems ($P = 0.064$) tended to improve, albeit not significantly, in the fexofenadine group.

In JRQLQ II by domain in each week, there was a significant improvement in the first week for all the domains in the fexofenadine group. No significant change was seen in the fexofenadine group for outdoor activities ($P = 0.055$) and sleep problems ($P = 0.064$) in the second week (end-point), which could have been due to changes in the pollen count (Fig. 6).

Symptom severity

The daily TSS (total score of sneezing, runny nose, nasal congestion, itchy eyes and watery eyes), as calculated from the subject diary, significantly improved in the fexofenadine group from the first day after administration compared with the placebo group. This improvement was sustained at the peak pollen count, showing improvement every day throughout the administration period (Fig. 7).

Safety

No serious adverse events were reported throughout the study period. There was no significant difference in the number of adverse events between the two groups ($P = 0.568$). A high white blood cell count and headache occurred most frequently.

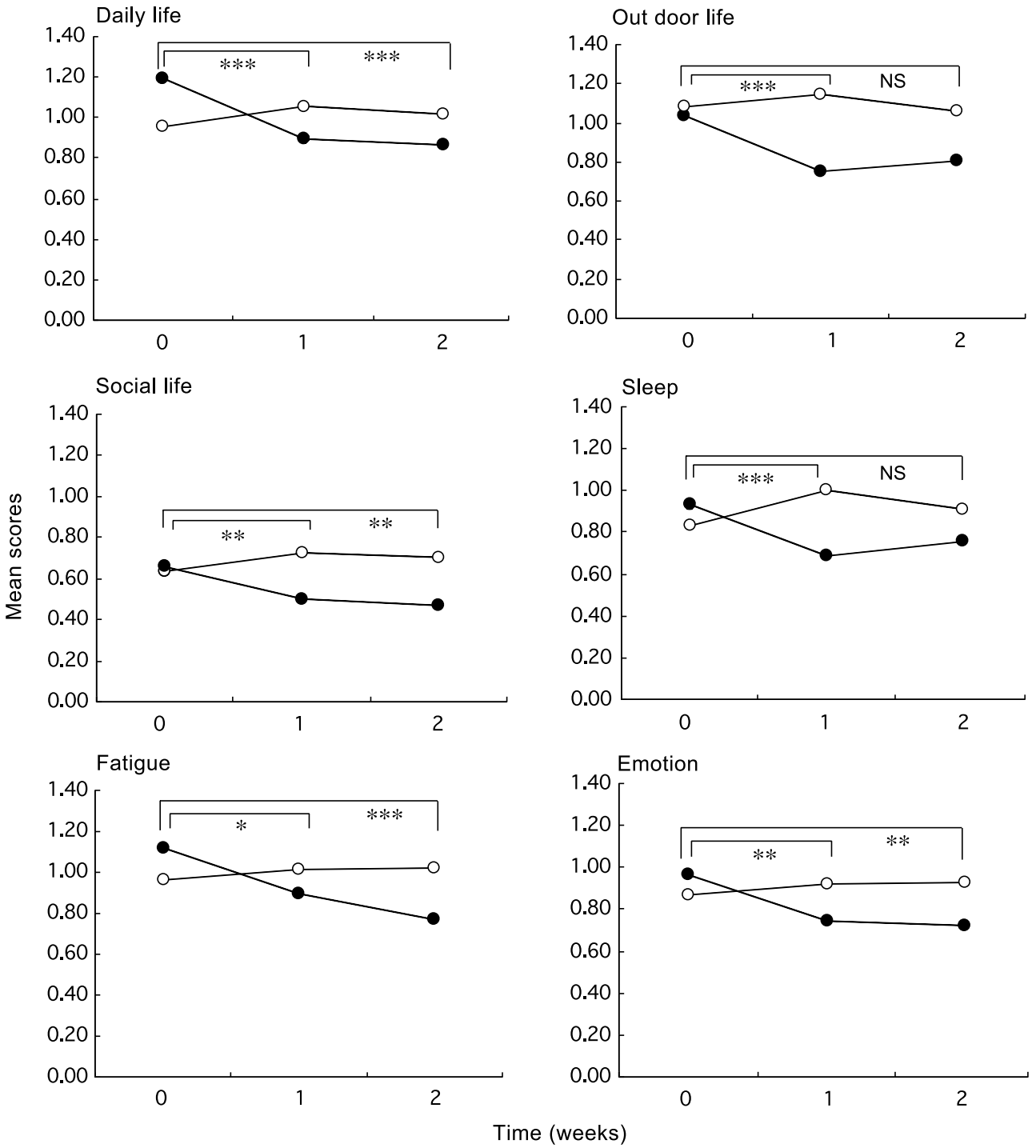


Fig. 6 Changes in quality of life-related questionnaire domains from baseline to end-point following 2 weeks administration of placebo (○) or fexofenadine HCL 120 mg (60 mg b.i.d.; ●). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with placebo.The starting day of administration (baseline), 1 week after the start of administration and 2 weeks after the start of administration (end-point) are indicated on the graphs as 0, 1 and 2 weeks, respectively.

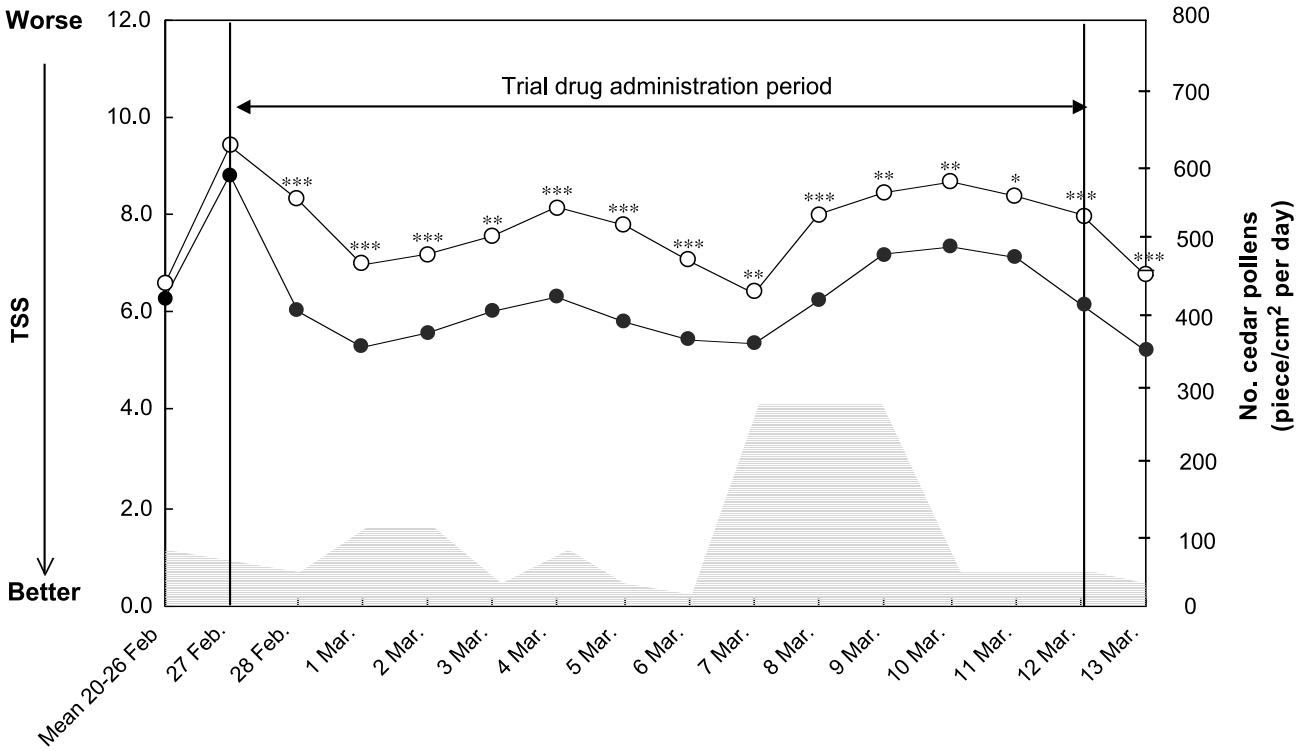


Fig. 7 Total symptom score (TSS) in subject diary and pollen counts following 2 weeks administration of placebo (○) or fexofenadine HCL 120 mg (60 mg b.i.d.; ●). The TSS included sneezing, nasal discharge, nasal congestion, itchy eyes and watery eyes. The number of cedar pollens throughout the 2 week period is indicated by the shaded area on the graph. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with placebo.

DISCUSSION

Allergic rhinitis has been regarded as a 'life style disease' that interferes with daily life rather than as a 'chronic disease'. This is based on the fact that allergic rhinitis is not a life-threatening disease but, rather, it worsens QOL. The World Health Organization defines QOL as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[3] To determine whether an improvement or deterioration of QOL has taken place, oral and written questionnaires are administered. Among the questionnaires that are currently used mainstream methods of surveying, some (SF-36 etc.) are not specific to particular diseases and examine general health status, whereas others examine QOL specific to a disease. From a survey using SF-36, Fukuroku *et al*.[3] reported that among nasal symptoms in perennial allergic rhinitis, nasal congestion was the one that interfered most severely with the QOL. The Juniper questionnaire is the only one specific to allergic rhinitis and is regarded as the standard questionnaire in the US and Europe.[4] Using this questionnaire, it has been reported that there is a correlation between the severity of disease and the QOL score of patients.[5]

We have recently developed and validated a Japanese original standardized questionnaire for allergic rhinitis.[6] The findings of the present study demonstrate that fexofenadine HCl 60 mg b.i.d. significantly improved the overall QOL and total symptom score in Japanese subjects with pollinosis compared with placebo during the 2 week treatment period. This improvement in QOL was associated with significant symptom relief in the fexofenadine treatment group. Furthermore, fexofenadine-treated subjects experienced significant improvement in nasal and eye symptoms, usual daily activities, social functioning, general physical problems and emotional function. These significant improvement scores ranged from 0.19 to 0.35 in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). This improvement rate is not consistent with the Juniper theory of 0.5.[7]

The results presented here are consistent with those published previously, in which fexofenadine significantly

improved QOL in pollinosis and chronic indiopathic urticaria (CIU) patients.[8–11] Tanner *et al*. assessed the impact of fexofenadine HCl 60 mg b.i.d. on patients' QOL in a pooled analysis of two placebo-controlled trials in patients with pollinosis.[8] A significant ($P = 0.05$) improvement in overall RQLQ score was reported for patients receiving fexofenadine HCl 60 mg b.i.d. compared with placebo.[8] In a more recent study, van Cauwenberge *et al*.[11] assessed the impact of once-daily administration of fexofenadine HCl 120 mg, loratadine 10 mg or placebo on patients' QOL in the treatment of pollinosis. A total of 509 pollinosis patients aged 12–75 years completed the QOL assessment (RQLQ). For all treatment groups (fexofenadine, loratadine and placebo), there was a significant improvement from baseline in overall QOL ($P < 0.0001$); however, the improvement in the fexofenadine group was significantly greater than that obtained in either the loratadine ($P = 0.03$ for fexofenadine *vs* loratadine) or placebo ($P = 0.005$ for fexofenadine *vs* placebo) groups. In addition, fexofenadine was significantly better than either loratadine or placebo in reducing overall mean 24 h reflective symptom scores for itchy, watery or red eyes and nasal congestion from baseline ($P = 0.05$), whereas the effect of loratadine on these two symptom scores did not differ from that of placebo.[11] Furthermore, in patients with CIU, fexofenadine HCl 60 mg b.i.d. significantly improved overall QOL compared with placebo.[9] These results corroborate the findings presented here that fexofenadine improved overall QOL in Japanese subjects with pollinosis.

The present clinical study demonstrated the usefulness of the recently validated JRQLQ instruments in assessing QOL in a Japanese patient population with pollinosis during the peak cedar pollinosis season. The JRQLQ, as a measure of QOL, will soon be adopted as an outcome measure for clinical trials in the Japanese population.[12] The results presented here support the use of the JRQLQ questionnaire for assessing the impact of pollinosis symptoms on QOL.

Conclusions

In conclusion, the present clinical study showed that fexofenadine HCl 60 mg b.i.d. significantly improves QOL in Japanese patients with pollinosis during the peak cedar pollenosis season, using a recently validated Japanese instrument.

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